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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,936	11/20/2003	Tod R. Smeal	034536-0220	6791

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,936	SMEAL ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *26-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/20/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The response filed on 11/21/05 to the restriction requirement of 10/20/05 has been received. Applicant has elected Group I, claims 1-25 for examination. Applicant has also selected "human", "breast cancer", "tumor tissue", and "whole fresh blood". Because applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Claims 1-62 are pending.

Claims 26-62 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-25 are currently under consideration.

The species elections are withdrawn.

Specification

The disclosure is objected to because it is unclear what the first two columns of Table 1 represent. The first column is unlabeled and the second column is labeled "Sample".

The specification is objected to on page 6, paragraph 22, for improper disclosure of polypeptide sequences, as it fails to comply with the requirements of 37 CFR 1.821

through 1.825. This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422). Proper correction is required.

Drawings

The drawings are objected to because, as presented, staining for PAK4 phosphorylation, hematoxylin, and eosin cannot be seen. Further, the drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because the specification describes Figures 1 and 2 as both having parts (a), (b), and (c) while the drawings only show Figure 1 (A.) and Figure 2 (B.) and (C.) (see paragraphs 31-32). Further, there appears to be no picture for Figure 2 C "Section of normal colon form patient", which is also not described in the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must

be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for reciting: "...a first PAK phosphorylation level..." Is the claim drawn to phosphorylation on specific amino acids of PAK or to the total amount of phosphorylation of PAK?

Claim 1 is further indefinite for reciting: "...wherein a lower level of PAK phosphorylation in the subsequent biopsy compared to the first biopsy is indicative of an

effect of the therapeutic composition..." Would an increased level of PAK phosphorylation in the subsequent biopsy not be indicative of "an effect"? Further, there is no definitive nexus between a lower level of PAK phosphorylation and any monitored effect.

Claims 7-8 are indefinite for reciting: "...suspected of containing cells capable of anchorage-independent cell growth." It is unclear what would make one "suspect" whether a sample contains cells capable of anchorage-independent cell growth.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as broadly claimed.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy

the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method of monitoring the effect of a therapeutic composition comprising measuring "a first PAK phosphorylation level" in a biopsy before administration of said composition, measuring "a second PAK phosphorylation level" in a biopsy after administration of said composition, and comparing the two phosphorylation levels to determine "an effect of the therapeutic composition" on a mammal. As broadly claimed, "a PAK phosphorylation level" encompasses changes in phosphorylation levels on *any* amino acid residue of *any* PAK family member, including those residues not involved in a family member's activation. Further, as broadly claimed, the claims encompass methods for monitoring a therapeutic involving biopsies from *any* mammal, including those without disease (see claim 1).

The specification teaches a phosphospecific anti-PAK4 polyclonal antibody, #108, which was raised against a fragment of PAK4 that was phosphorylated on serine-474 (paragraph 52, in particular). The specification further states that phosphospecific

antibodies directed against serine-474 detect activated PAK4 (paragraph 4). The specification further states that "The data for the phosphospecific antibody (#108) in colon carcinomas is especially informative (6 out of 6 patients showed marked perinuclear staining in tumor and not distal benign tissue....This result strongly suggests that PAK4 is specifically active in colon tumor cells and inactive in benign colon tissue from the same patient. Staining of phosphorylated PAK4 was also observed in renal cell carcinoma, lung adenocarcinoma, prostatic adenocarcinoma, intraductal breast adenocarcinoma, and ovarian adenocarcinoma" (paragraph 80). The specification further states: "In tumors, strong staining with phosphospecific-PAK4 antibody was identified in colonic adenocarcinomas (while distal benign tissue failed to show phospho-PAK4 staining). On a scale of 0-3, "0" indicates no staining, "1" is indicative of weak staining, "2" indicates moderate staining and "3" indicates strong staining. Adenomatous epithelium was faintly to moderately positive, but most normal epithelium showed only staining of "1" for phosphorylated PAK4. Prostatic adenocarcinoma showed moderate staining ("2")" (paragraph 81). The specification further states: "In benign tissues, the most prominent staining for phosphorylated PAK4 was seen in adeipocytes, cardiac myocytes, sebaceous glands, and occasional macrophages. Additional positive cell and tissue types included hair follicles, benign prostatic epithelium, breast epithelium, and urothelium" (paragraph 82).

Though the data are not explicitly shown, the specification suggests that phosphorylation of PAK4 on ser-474 is indicative of colon carcinoma, where

phosphorylation of PAK4 is described as being found in tumor and not in distal benign tissue (paragraph 80, in particular). However, the disclosure that breast epithelium stains positively for phosphorylated PAK4 indicates that the claimed method would not work with *the elected invention* of breast cancer. Further, the specification provides **no working examples** of the claimed invention, thus it is unclear whether a decrease in PAK4 phosphorylation would result in any kind of *therapeutic effect.* The specification only provides general guidelines or prophetic teaching of how changes in PAK phosphorylation levels could be used to monitor an undisclosed effect of a therapeutic composition (paragraph 9, in particular).

As evidenced by Qu et al (Molecular and Cellular Biology, May 2001, 21(10):3523-3533), PAK4 differs from other members of the PAK family in both sequence and function. For instance, PAK4 lacks several key features characteristic of PAKs 1, 2, and 3, including four praline-rich motifs, an autoinhibitory domain, and a putative G $\beta\gamma$ binding site (page 3524 left column, in particular). Further, "Unlike the other PAKs, Pak4 interacts with the effector loop mutant Cdc42C40" (page 3524 left column). Further, Qu et al states: "In contrast to other PAKs, we have found that activated PAK4 confers anchorage-independent growth on fibroblasts and leads to focus formation on soft agar assays" (page 3532 left column, in particular). Therefore, one of skill in the art would not reasonably assume that phosphorylation of PAK4 on ser-474 is indicative of activation, or phosphorylation, of any other PAK family member.

Colon carcinoma is the only ailment of which the disclosure demonstrates that PAK4 phosphorylation on ser-474 is indicative. If a molecule such as phosphorylated PAK4 is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some phosphorylation pattern that would allow the claimed phosphorylated polypeptide to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly

described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Due to the unpredictability of the art, one of skill in the art would only predictably be able to use PAK4 phosphorylated on reside Ser-474, but not any other PAK family member or any other phosphorylated reside of PAK4, in a diagnostic setting for colon carcinoma.

In view of the teachings above, and the lack of guidance or exemplification in the specification, it would not be predictable that the method would function as broadly contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as broadly claimed. For the reasons above, Applicant only appears to be enabled for a method for monitoring the effect of a therapeutic composition on a mammal that has colon cancer, comprising measuring a first phosphorylation level of PAK4 on ser-474 before administration of a therapeutic composition to said mammal, and measuring a second phosphorylation level of PAK4 on ser-474 in a subsequent biopsy obtained from said mammal after administration of the therapeutic composition, wherein a lower level of PAK phosphorylation on ser-474 in the subsequent biopsy compared to the first biopsy indicates that the therapeutic composition decreases PAK4 activation.

Summary

No claim is allowed.

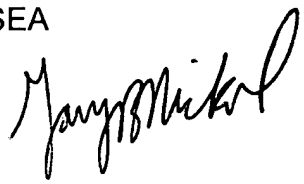
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA



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